Functional and Anatomical Aspects of Prefrontal Pathology in Schizophrenia

by Manuel F. Casanova

Abstract

Neuropathology is a field that correlates autopsy findings to clinical symptomatology. Since the brain has an inordinate number of parcelled regions, each having a different function, it makes more sense to work in an inverse fashion and use clinical findings to establish pathological correlations. In this regard, a lesion in the prefrontal lobes can explain some of the salient findings in schizophrenia, for example, scrambled language, disordered thinking, and abnormal behavior. Recent quantitative cytoarchitectural observations by Goldman-Rakic and Selemon sustain such a correlation. By using a computerized image analysis system, these authors have described an abnormally high neuronal density and reduced cortical thickness in many of their patients with schizophrenia. The importance of these findings is discussed in terms of the recent schizophrenia literature.


In 1952, many of the world’s leading researchers gathered at the First International Congress of Neuropathologists in Rome. Regardless of the approximately 250 pertinent studies that had been published by then, it became clear that there was no agreement as to specific histological findings that could account for schizophrenia. The issue was not whether a lesion was present, but which of all of those reported were significant. Neuropathological lesions of a developmental or acquired nature are commonly seen in the brains of schizophrenia patients (Bruton et al. 1990). Despite the wide array of histopathological lesions (David 1957; Jellinger 1985), none have thus far proven diagnostic. Perhaps it is not the nature of the lesion but its location that is crucial in lowering the threshold for expressing certain schizophrenia symptoms in genetically susceptible individuals. If this is the case, why should we consider the frontal lobe to be an important pathology site in schizophrenia?

According to Goldman-Rakic and Selemon (1997, this issue), the prefrontal lobe acts as a clipboard, holding on to information needed to guide ongoing behavior. Psychologists call this function “working memory.” The frontal lobe exhibits different working-memory domains, according to the anatomical areas involved. Visuospatial processing is performed by the dorsolateral prefrontal cortex. Working memory for the features of objects and faces occurs in more lateral and inferior cortices, while semantic encoding and retrieval involves still more inferior and insular regions.

It is easy to envision how a defect in working memory could promote the expression of schizophreniform symptomatology such as scrambled language, disordered thinking, and abnormal behavior. In addition, frontal lobe lesions may cause additional multifaceted symptomatology, based on the rich connectivity of this site to other brain regions. This possibility was predicted by Nauta (1962), who believed that the amygdala, prefrontal cortex, and inferior temporal lobe constitute a distinct functional and anatomical system. It is therefore not surprising that lesions of the prefrontal cortex in monkeys have also been associated with pacing, hyperactivity, social withdrawal, and a gross deficit in sorting sensory information in complex environments (Kling 1975). In essence, as Goldman-Rakic and Selemon are careful to point out, we cannot separate the function of the prefrontal lobe from the rest of the brain.

Despite the vast literature implicating the frontal lobes in the pathogenesis of schizophrenia, there have been few reproducible histological findings. I am reminded that not long ago, in reviewing the existing neuropathological data, Plum (1972) stated that schizophrenia was the “graveyard of neuropathologists.” He emphasized that new quantitative approaches should be considered and introduced to schizophrenia research. In
the present article, Goldman-Rakic and Seelen discuss some of their recent findings using a three-dimensional counting method of Brodmann’s area 9 in the prefrontal cortex of schizophrenia patients. With this new and sensitive methodology, they have been able to describe an abnormally high neuronal density and reduced cortical thickness in many of their patients. The authors suggested that prefrontal cortex neurons were dystrophic with consequent degeneration of their projections. Although this seems the most plausible conclusion, I will offer one word of caution. In their often-quoted article on the ventral cochlear nuclei, Konigsmark and Murphy (1972) were unable to find a predictable correlation between reductions in nuclei volume and the total number of neurons. It is evident that additional changes in the neuropil (e.g., myelin, glial cells, blood vessels, extracellular space) should be excluded from histological volume studies before the possibility of neuronal pathology is considered.

Goldman-Rakic and Seelen’s finding of dystrophic neurons and processes receives some support from quantitative immunolabeling and neurochemical studies. Significant reductions of synapsin binding have been observed in selected brain areas of some schizophrenia patients (Browning et al. 1993). Not surprisingly, the abnormally regulated neurotransmitter release is thought to be dopamine; [3H]GBR 12935 binding data (a measure of the dopamine transporter) shows a differential binding with age in the prefrontal cortex of patients with schizophrenia (Hitri et al. 1995). Quantitative electron microscopic studies again suggest that the basis of this abnormality is at the synaptic level (Uranova 1988).

Building a story out of the evidence presented in this article is a daunting task, but two items seem well worth mentioning. First, thermal lesioning experiments of the ventral tegmental area in neonatal rats have shown reduction in the cortical thickness of dopaminergic terminal projection zones (Kalsbeek et al. 1987). The results suggest a neurotrophic role for dopamine early in life.

Second, a neuropathological report in a case of childhood schizophrenia indicated central chromatolysis and gliosis in a restricted distribution of the brainstem and thalamus (Casanova et al. 1990). Cell loss, cytoarchitectural disruption, and dystrophic neurons were evident in the frontal lobes, piriform cortex, and entorhinal region. The neuropathological findings were interpreted as consistent with an early onset disturbance of dopaminergic neurons in the rostral brainstem and secondary involvement of their terminal projection sites (e.g., prefrontal, piriform, and entorhinal cortex). It can therefore be suggested that a developmental defect of dopaminergic transmission leads to degenerative synaptic changes in terminal fields, including the prefrontal cortex.

I would like to end the discussion of Goldman-Rakic and Seelen’s article by summarizing some pertinent articles with the rich literature on the neuropathology of schizophrenia. In one of the earliest studies, Meynert (1884) attributed the genesis of psychotic symptomatology to atrophy of the frontal lobe. The general notion in Meynert’s time was that atrophy resulted from the gradual waning of tissue energy, a process called abiotrophy by Gowers (1902). A histological correlate to the abiotrophic process was found in schizophrenia when Alzheimler (1913) described changes consistent with pigmentary degeneration. Analogous changes were later added to the medical literature by the Vogts and their disciple Von Buttlar-Brentano (1952). Vogt and Vogt (1952) showed a variety of wasting cells from patients with catatonia. Many of the salient examples of dwarf neurons came from the cingulate and prefrontal cortex. These investigators insisted that it was the persistence of diseased cells, rather than their loss, that caused schizophrenia symptoms (Colon 1972). Von Buttlar-Brentano observed similar shrunken cells for the nucleus of the substantia innominata of Meynert (1884) in patients with catatonia but not in other subtypes of schizophrenia.

Isolated findings such as the presence of dwarf cells or synaptic aberrations have little meaning when not correlated with any clinical signs or symptoms. By neglecting to use correlation studies, we follow in the footsteps of Br’er Rabbit in Uncle Remus’ tale. In this story, Br’er Rabbit was snared by Br’er Fox using a tar baby as a bait. Br’er Rabbit repeatedly struck the unresponsive and seemingly rude baby only to become more entrapped in the tar with each blow (Ober 1987). Reporting isolated neuropathological findings is one of the few instances where practice doesn’t make better. The major contribution of the present article is that the morphological findings, if not new, can be placed in proper perspective with those clinical findings we often see in patients with schizophrenia. As Plum (1972) aptly stated some 25 years ago, the introduction of new techniques, such as the one discussed in this article, may help solve the neuropathological puzzle of schizophrenia.

References


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